REMARKS

Claims 1, 2, 4, 5, 8, and 22 are pending in the application. Claim 4 stands withdrawn. Claims 1, 2, 5, 8, and 22 are currently under examination.

35 U.S.C. § 112, first paragraph, enablement, rejections

Claims 1, 2, 5, 8, and 22 were rejected under 35 U.S.C. § 112, 1st paragraph, allegedly because undue experimentation is needed to practice the invention.

According to the Office Action the specification is enabling for a method of identifying an increased likelihood of lupus nephritis in a mouse by comparing the midkine mRNA expression level in the kidney of a mouse with that of a control mouse. The Office Action considers that the specification is not enabling for methods to diagnose lupus in a human by comparing the expression level of midkine in a kidney of a human of interest with that of a control human.

Without regard to the teachings of the specification and the 1.132 declaration submitted with the response filed 23 October 2007, the Office Action asserts that Applicants have not overcome the 35 U.S.C. § 112 enablement rejection of claims 1, 2, 5, 8, and 22. Applicants respectfully traverse these rejections.

Throughout, the Office Action stresses that the issue is whether the midkine gene expression pattern seen in the mouse model can be extrapolated to human and whether midkine expression can be used predictably to determine the likelihood of lupus in human. At page 16, the Office Action incorrectly asserts that Liu "...found that there was no overlap between the differentially expressed genes between human and mouse data sets with regard to systemic lupus." The Office Action then, at page 17, uses this incorrect assertion as a basis to conclude that there is "unpredictability in extrapolating the findings in the specification in a mouse model to humans."

The Office Action incorrectly applies Liu (Clin. Immunol. 2004, 112:225-230) to support the conclusion that there is a lack of correlation between genes differentially expressed in lupus nephritis mouse models with humans suffering of lupus nephritis. While Liu did not find any overlapping differentially expressed genes between human with insulin-dependent diabetes mellitus (IDDM) and non-obese diabetic (NOD) mice, Liu found that there were two overlapping differentially expressed genes (DEGs) between humans with systemic lupus erythematosus (SLE) and New Zealand Mixed (NZM) mice. Page 228, first column, first paragraph of Liu reads:

> "When we compared human **IDDM with NOD** mouse data, we **did not find** any **overlapping** DEGs between human and mouse data sets. We compared the DEGs in **SLE to our NZM** microarray data set and found **two overlapping DEGs** (Figs 2C and D)."

Thus, Applicants respectfully submit that, contrary to the Office Action's assertions, Liu found that there is a correlation between differentially expressed genes in a mouse model of lupus nephritis and humans suffering of lupus nephritis.

At page 21, the Office Action concludes with "...midkine gene expression and correlation to susceptibility in lupus would have to be determined in a human population. This would require many intervening steps without predictable success...[and]...it would be unpredictable that an increase in the midkine gene in the mouse model would be correlative to an increase in a human sample." In light of the Applicants teachings, Applicants respectfully submit that it would be predictable that an increase in the midkine gene in the mouse model would be correlative to an increase in a human sample. Applicants submit that the state of the art and the specification as filed are enabling for a method of identifying increased likelihood of lupus nephritis in a human by comparing the midkine mRNA expression level in the kidney of the human with that of a control human.

As stated on MPEP § 2107.03, a reasonable correlation between the activity in question and the asserted utility is all that is needed. Paragraph **[0067]** of the specification as filed states that "...overexpression of midkine contributes to protection from cell death and induces phosphorylation of Akt 1 in **human** tissues." Akt1 holds a pivotal upstream role in controlling the **mammalian** target of rapamycin (mTOR) pathway. A statistical test of the overlap of the mTOR pathway with genes published in literature for human lupus indicates that proteins that interact with the mTOR pathway show a highly significant association with human lupus. In addition, therapeutic administration of rapamycin, an mTOR inhibitor, to patients with clinically active SLE has been shown to be efficacious (Fernadez, D. et al. 2006, Arthritis Rheum. 54:2983-2988 enclosed as Exhibit A.) In the specification as filed, Figure 4 and paragraph **[0058]** describe restoration of midkine expression to normal levels after therapeutic administration of rapamycin in the diseased NZB X NZW F1 mice.

Thus, there exists strong evidence that mTOR deregulation is seen in humans with lupus nephritis and that midkine's control of Akt1, at the initiation of the mTOR pathway, renders it a good choice as a therapeutic candidate. In addition, the teachings in the specification indicate that midkine plays a very early role in the lupus nephritic phenotype in mouse models, consistent with the role of midkine in controlling the mTOR pathway.

MPEP § 2107.03 also states that "[i]f reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process." Applicants submit that the specification as filed, together with the knowledge in the art demonstrate that midkine expression is correlated with human susceptibility to lupus.

Accordingly, Applicants submit that those of skill in the art would recognize that the results obtained with the mouse models used in the present application are applicable to humans for the reasons noted. In view of the foregoing, withdrawal of the rejection under 35 USC § 112, first paragraph, is respectfully requested.

CONCLUSION

In view of the above comments, Applicants respectfully submit that the Application is in form of allowance. If any outstanding issue remains, the Examiner is invited to contact the undersigned agent.

During the pendency of this application please treat any reply requiring a petition for extension of time for its timely submission as containing a request therefore for the appropriate length of time. The Commissioner is hereby authorized to charge all required extension of time fees during the entire pendency of this application to Deposit Account No. 01-1425.

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